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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,036	03/22/2006	Osamu Cynshi	CYNSHI 7	4404

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EXAMINER	
KEYS, ROSALYND ANN	

ART UNIT	PAPER NUMBER
1621	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,036	CYNSHI ET AL.	
	Examiner	Art Unit	
	Rosalynd Keys	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 17-35 are pending.

Claims 17-35 are rejected.

Claims 1-16 are cancelled.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 34 and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Krieger et al. (US 2004/0006129 A1).

Krieger et al. teach the use of the compound 2, 3-dihydro-5-hydroxy-2, 2-dipentyl-4, 6-di-tert-butyl-benzofuran for the treatment of myocardial infarction and cholestasis (see abstract, paragraphs 0007 and 0011, and claims 1, 3 and 6). Cholestasis is any condition in which bile excretion from the liver is blocked (see paragraph 0007). Some causes of cholestasis include primary bilary cirrhosis, primary sclerosing cholangitis, and viral hepatitis (A, B. C, etc.). It is known that that the blood levels of the enzyme AST is increased in cases of hepatitis. AST is also known to be increased in myocardial infarction. Thus, based upon the teachings of Krieger et al. one having ordinary skill in the art would reasonably believe that a reduction in the amount

of AST leaking from liver cells into the blood would inherently occur during treatment of myocardial infarction and cholestasis with the compound 2, 3-dihydro-5-hydroxy-2,2-dipentyl-4,6-di-tert-butyl-benzofuran.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 17-35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (US 5,574,178) in view of Tsujii et al (US 5,043,354).

The instant claimed invention is directed to the use of compounds of formula 1 (shown in clam 1) to treat fatty liver or hepatic diseases.

Tamura et al teach a genus which embraces the compounds used in the instant claims (see columns 1-10). Specific compounds having the claimed formula (1) are disclosed in columns 13-15. The compound 4,6-di-t-butyl-5-hydroxy-2,2-di-n-pentyl-2,3-dihydrobenzofuran as disclosed in new claim 35 is expressly disclosed in column 15 as compound x. Tamura discloses that the compounds have antioxidant properties and are useful for treating arteriosclerosis, myocardial infarction and other ischemia diseases (see column 1, lines 9-46 and column 2, line 54 to column 3, line 23).

Tamura fails to explicitly teach that the compounds could be useful for treating fatty liver or hepatic diseases.

Tsujii discloses benzofuran compounds that are useful in the treatment of diseases causes by reactive oxygen species (see column 1, lines 9-12), which means that these compounds are antioxidants. Tsujii list ischemic diseases and myocardial infarction as typical diseases that can be treated with the benzofuran compounds (see column 1, lines 35-46). Tsujii also listed disorders of the liver as diseases that would be

treatable using the benzofuran antioxidants. Thus Tsujii establishes that ischemia, myocardial infarction and disorders of the liver are treated by the same method.

It would have been obvious to one having ordinary skill in the art at the time that applicant's invention was made to have used the compounds of Tamura to treat disorders of the liver, as taught by Tsujii. Fatty liver and hepatic diseases are subgeneric to the phrase disorders of the liver. Thus a skilled artisan would have had a reasonable expectation of success in using the compounds in Tamura in the treatment of fatty liver and hepatic diseases including aspartate aminotransferase leaking from the liver cells into the blood. One skilled in the art would have been motivated to use the compounds in Tamura to treat other diseases which are affected by the same mechanism. ***"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solution, a person of ordinary skill in the art has good reason to pursue the know options within his or her technical grasp" (SUPREME COURT OF THE UNITED STA TESS, KSR INTERNATIONAL CO. v. TELEFLEX INC. et al, April 30, 2007; 550 U.S. 2007)***.

8. Claims 17-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cynshi et al. (US 6,133,279) in view of Ookawa et al. (JP 01213276A).

Cynshi et al. teach a compound having the claimed formula (1) for use as an antioxidant which inhibits against lipid peroxidation (see entire disclosure, in particular column 1, line 5 to column 2, line 67; column 5, line 65 to column 7, line 29; column 15, lines 18-28; and Tables 1 and 2 in columns 33 and 34). Cynshi et al. teach that the compounds having the claimed formula 1 are useful as a preservative for the liver (see

column 15, lines 18-28). The compound 4,6-di-t-butyl-5-hydroxy-2,2-di-n-pentyl-2,3-dihydrobenzofuran as disclosed in new claim 35 is expressly disclosed in column 7, lines 57-58.

Although Cynshi et al. teach the compounds having the claimed formula 1 are useful as a preservative for the liver, they do not expressly teach the use of the compounds having the claimed formula 1 for the treatment of fatty liver or hepatic diseases, which include aspartate aminotransferase leaking from the liver cells into the blood.

Ookawa et al. (JP 1-213276) teach a benzofuran derivative of the formula (I), which is useful for treatment or prophylaxis of dysfunction of heart, brain, lung, kidney or liver (see attached Derwent abstract). It is further taught that since (I) inhibits lipid peroxidation, 5-lipoxygenase, thromboxane A2 synthetase or oxygen-derived free radical generation, they can be used for treatment of prophylaxis of thrombosis, ischaemic disease (e.g., myocardial infarction, cerebral apoplexy), nephritis, lung insufficiency, asthma, psoriasis vulgaris, inflammation, immediate allergy, atherosclerosis, fatty liver, hepatitis, liver cirrhosis, immunodeficiency, tumours, etc.

It would have been obvious to one having ordinary skill in the art at the time that applicant's invention was made to have used the compounds of Cynshi et al. to treat liver or hepatic diseases, such as those taught by Ookawa et al., since like the compounds of Ookawa et al., the compounds of Cynshi et al. are antioxidants which inhibit lipid peroxidation. Thus a skilled artisan would have had a reasonable expectation of success in using the compounds in Cynshi et al. in the treatment of fatty

liver and hepatic diseases including aspartate aminotransferase leaking from the liver cells into the blood. One skilled in the art would have been motivated to use the compounds in Cynshi et al. to treat other diseases which are affected by the inhibition of lipid peroxidation. ***"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solution, a person of ordinary skill in the art has good reason to pursue the know options within his or her technical grasp" (SUPREME COURT OF THE UNITED STA TESS, KSR INTERNATIONAL CO. v. TELEFLEX INC. et al, April 30, 2007; 550 U.S. 2007)***.

Response to Arguments

9. Applicant's arguments filed April 9, 2009 have been fully considered but they are not persuasive.

The Applicants again submit, using for support the teachings of Spaniol et al., that one skilled in the art would not have expected from the disclosures of Tamura et al. and Tsujii et al. that the compound of claim 17 is useful for the treatment of fatty liver or hepatic disease.

This submission is not persuasive because the preponderance of evidence shows that benzofuran compounds as well as antioxidants have been successfully used in the treatment of various hepatic disorders (see just a few of the references below).

1) Masazumi et al. (JP 05-320169), which teach a benzofuran derivative is taught to exhibit an action to inhibit the increase in the activity of ALT and is useful for the prevention and treatment of hepatopathy (see entire computer generated English

translation, in particular paragraphs 0002-0010). It is also taught that the hepatopathy depressant, which is the benzofuran derivative expressed with formula (I) is safe for Homo sapiens (see paragraph 0049).

2) Royer et al. (US 3,808,236), which teach that the compounds 3, 5, 6-trimethyl-2-nitro-benzofuran (R 4906) and 2-nitro-benzofuran (R 5144) can be used in therapy for the treatment of hepatic amoebiasis (see column 2, lines 38 and 39; column 6, lines 14 and 15; and column 9, lines 9-12). Hepatic amoebiasis is a well known infection of the liver with a single-celled parasite called Entamoeba histolytica.

3) Ookawa et al. (JP 1-213276), which teach a benzofuran derivative which is useful for treatment or prophylaxis of dysfunction of heart, brain, lung, kidney or liver (see attached Derwent abstract).

4) Cynshi et al. (US 6,133,279), which teach a compound having the claimed formula for use as a preservative for the liver (see entire disclosure, in particular column 5, line 65 to column 7, line 29; column 15, lines 18-28; and Tables 1 and 2 in columns 33 and 34).

5) Adelman et al. (WO 9825627 A1), which teach the use an antioxidant for the treatment of viral or chronic active hepatitis (see attached Derwent abstract).

6) Hayashi et al. (JP 11349526 A), which teach the use an antioxidant agent for the treatment of hepatitis (see attached Derwent abstract).

7) Allegrini et al. (WO 9940066 A1), which teach the use an antioxidant for the treatment of hepatic disorders (see attached Derwent abstract).

8) Carson et al. (WO 9814181 A1), which teach the use of an antioxidant for the treatment of hepatitis and other forms of hepatic fibrosis (see attached Derwent abstract).

9) Ortenburger et al. (DE 19929993A1), which teach the use an antioxidant and radical scavenger as a hepatic drug, especially for treating liver cirrhosis, chronic hepatitis, liver parenchymal damage, and fatty liver (see attached Derwent abstract).

10) Krieger et al. (US 2004/0006129 A1) teach the use of the compound 2, 3-dihydro-5-hydroxy-2, 2-dipentyl-4, 6-di-tert-butyl-benzofuran for the treatment of myocardial infarction and cholestasis (see abstract, paragraphs 0007 and 0011, and claims 1, 3 and 6). Cholestasis is any condition in which bile excretion from the liver is blocked (see paragraph 0007).

Based upon the teachings of at least these 10 references as well as those disclosed by Tamura et al. in view of Tsujii et al., the compound of claim 17 would have been expected to be useful for the treatment of fatty liver or hepatic disease.

The Applicants submit that neither Tamura nor Tsujii mentions leakage of aspartate aminotransferase (AST) from the liver cells into the blood, thus one skilled in the art would never have been motivated to use the compounds in Tamura to reduce the leakage of aspartate aminotransferase from the liver cells into the blood before the priority date of the present application.

This argument is not persuasive because it is known that liver enzymes such as AST leak out into the bloodstream in conditions in which hepatocytes are damaged or die (see for instance paragraph 0132 of US 2005/0058735 A1). For example, the blood

levels of AST increases in cases of hepatitis. Thus, one having ordinary skill in the art would reasonably expect that treatment of hepatitis would result in a reduction of AST in the bloodstream.

The Applicants submit that the identifiable solutions in Tamura and Tsujii are compounds that are anti-oxidants. The methods claimed herein, on the other hand, inhibit leakage of liver enzymes into the blood. This has nothing to do with oxidative stress, and therefore one skilled in the art would not be motivated to choose from the Tamura or Tsujii compounds to treat conditions in which enzymes leak from the liver into the blood.

This argument is not persuasive because as discussed above antioxidants as well as benzofuran compounds have been shown to be useful in the treatment of hepatic diseases as well as fatty liver. The compounds of Tamura are benzofuran compounds and function as antioxidants. Hepatitis is a hepatic disease that has been successfully treated with both antioxidants as well as benzofuran compounds. As discussed above the blood levels of AST increases in cases of hepatitis. Thus, one having ordinary skill in the art would reasonably expect that treatment of hepatitis would result in a reduction of AST in the bloodstream.

The Applicants submit that one skilled in the art appreciating the great structural differences between the compounds of Cynshi and Oogawa would not apply the teachings of Ookawa to those of Cynshi.

This argument is not persuasive because although there are some structural differences between the compounds of Cynshi and Oogawa the most significant

structure of the compounds of Cynshi and Oogawa is the benzofuran group which is common to both as well as the fact that the compounds of both have antioxidant properties. Thus, like the compounds of Oogawa, the compounds of Cynshi have a benzofuran group and antioxidant properties. Therefore, the ordinary skilled artisan would have a reasonable expectation that the compounds of Cynshi would be useful for treating the same conditions as the compounds of Ookawa.

The Applicants submit that one skilled in the art would not look to antioxidants as disclosed by Cynshi and Ookawa to treat fatty liver and liver diseases caused by aspartate aminotransferase or other liver enzymes form leaking from the liver cells into the blood.

This argument is not persuasive because as discussed above antioxidants as well as benzofuran compounds have been shown to be useful in the treatment of hepatic diseases as well as fatty liver. The compounds of Cynshi are both an antioxidant as well as a benzofuran compound. Hepatitis is one such hepatic disease that has been successfully treated with both antioxidants as well as benzofuran compounds, as taught by Ookawa. As discussed above the blood levels AST increases in cases of hepatitis. Thus, one having ordinary skill in the art would reasonably expect that treatment of hepatitis would result in a reduction of AST in the bloodstream. Thus, one skilled in the art would look to antioxidants as disclosed by Cynshi and Ookawa to treat fatty liver and liver diseases caused by aspartate aminotransferase or other liver enzymes from leaking from the liver cells into the blood.

For at the above reasons as well as those disclosed in the previous office action, mailed January 13, 2009, claims 17-35 are considered to be prima facie obvious.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosalynd Keys whose telephone number is (571)272-0639. The examiner can normally be reached on M & T 5:30 am-7 am & 9:30 am-4:30 pm: W-F 8:00 am-4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Sullivan can be reached on 571-272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rosalynd Keys/
Primary Examiner, Art Unit 1621

June 24, 2009